
Faster Gradients for Semiempirical Methods

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ABSTRACT: A new algorithm for the numerical evaluation of gradients in semiempirical methods is described. The method is approximately twice as fast as the schemes currently employed and produces gradients of comparable accuracy. This method has been tested by comparing the results obtained by the new method with those of the previous numerical scheme, and also with those calculated analytically. The results of using the new gradients in geometry optimizations are also presented. © 1999 John Wiley & Sons, Inc. *J Comput Chem* 20: 629–635, 1999

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Introduction

Semiempirical self-consistent field (SCF) methods were originally developed, because, for systems of meaningful size, it was impossible to solve the underlying equations without approximation. Although this is no longer true, use of semiempirical methods is actually increasing rather than decreasing,^{1,2} and there are active research programs aimed at extending their range of applicability.³ The reasons for this are twofold: first, the much faster speed of semiempirical methods; and, second, the fact that in many cases the results from

a well-parameterized semiempirical method may actually agree better with experiment than those from an *ab initio* calculation with small basis set/low level of theory. Moreover, semiempirical methods will always have a place as a precursor to more expensive calculations, providing initial guess geometries, Hessians, etc.

Recently, the appearance of so-called “linear scaling” semiempirical methods^{4–7} has opened up a new era in computational chemistry, making it possible to use ordinary workstations to perform semiempirical calculations on molecules containing thousands of atoms. Direct transfer, however, of the techniques developed for computations on small- to medium-sized molecules, to very large systems is not without problems. For example, a geometry optimization on the small protein, crambin (containing 640 atoms), required modification

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to both the standard BFGS optimization procedure and the coordinate system used to improve convergence—even then it required several thousand steps.⁸

Usually, for closed-shell and unrestricted open-shell semiempirical calculations the time required for evaluation of the gradient is small compared with the time required to converge the SCF energy. During a geometry optimization, however, only a few iterations are required in each SCF and, as a consequence, the relative time spent evaluating the gradient is much larger. For example, the first SCF computation of the valinomycin molecule (168 atoms) requires 36 seconds on a Sun Ultra Sparc workstation. The gradients calculation uses 7.6 seconds, or 17% of the total time. During geometry optimization, the gradients calculation time increases to approximately 30%. In light of this, and the large number of gradient calculations required to optimize the structure of large molecules, we investigated ways of decreasing the time required to evaluate semiempirical gradients. In this article we outline a simple modification to the numerical gradient algorithms routinely used in semiempirical codes. The modification produces gradients of similar accuracy to those normally computed, but requires approximately half the time. The new algorithm is contrasted with the traditional approach and with the use of analytical gradients.

Method

Most popular semiempirical methods, such as MNDO,⁹ AM1,¹⁰ and PM3¹¹ are based on the neglect of diatomic differential overlap (NDDO) approximation.¹² For such methods, the total energy can be written as a sum of one and two atom contributions associated with either the SCF or core repulsion part of the total energy¹³:

$$E_{total} = E1_{scf} + E2_{scf} + E2_{core} \quad (1)$$

For obvious reasons, the gradient depends only on the two atom energy terms ($E2$), and can therefore be evaluated by adding together atom pair derivative energies. This method is used in MOPAC¹⁴ and other popular semiempirical programs.^{15,16}

Traditionally, the atom pair derivative energies are evaluated numerically, because previous attempts to implement analytic formulas have proven

to be too computationally expensive.¹⁷ In MOPAC, there are two options for numerical gradient evaluation.¹⁰ The default option evaluates pair energies at the following four coordinates ($\Delta x - 0.5\delta$, $\Delta y - 0.5\delta$, $\Delta z - 0.5\delta$), ($\Delta x + 0.5\delta$, $\Delta y - 0.5\delta$, $\Delta z - 0.5\delta$), ($\Delta x - 0.5\delta$, $\Delta y + 0.5\delta$, $\Delta z - 0.5\delta$), and ($\Delta x - 0.5\delta$, $\Delta y - 0.5\delta$, $\Delta z + 0.5\delta$), and uses these to obtain the atom pair derivative. The resulting derivatives are accurate to first order, and may be likened to those obtained by a one-sided finite difference scheme. This scheme requires the pair interaction energy to be evaluated four times for each atom pair. The alternative "PRECISE" option uses a two-sided finite difference scheme, requiring the pair energy to be computed six times for each atom pair.

In what follows, we show that it is possible to reduce the computational cost required to form the derivative pair energies by evaluating the derivatives with respect to interatomic distance instead of Cartesian coordinates. The general idea is based on the observation that, for any function, $T(R)$ (where R is the interatomic distance), the derivative with respect to coordinate m can be expressed as:

$$\frac{\partial T(R)}{\partial m} = \frac{\partial T(R)}{\partial R} \times \frac{\partial R}{\partial m} \quad (2)$$

where $\partial R/\partial m$ equals $\Delta x/R$, $\Delta y/R$, or $\Delta z/R$, for m equal to x , y , or z , respectively. Applying this relationship to the computation of $\partial E2_{core}/\partial m$ is trivial, because $E2_{core}$ depends only on internuclear distance. Unfortunately, this is not the case for $E2_{scf}$, which depends both on interatomic distance and atomic orientation.

For closed-shell and unrestricted open-shell SCF calculations the derivative of the $E2_{scf}$ with respect to coordinate m is given by:

$$\begin{aligned} \frac{\partial E2_{scf}}{\partial m} = & \sum_{i,j} \sum_B P_{ij} Z_B \frac{\partial [ij|ss_B]}{\partial m} \\ & + \sum_{i,k} P_{ik} \beta_{ik} \frac{\partial S_{ik}}{\partial m} \\ & + \sum_{i,j,k,l} \frac{\partial [ij|kl]}{\partial m} D_{ij,kl} \end{aligned} \quad (3)$$

where indices i, j, k, l represent molecular orbitals, Z_B is the core charge on center B , β_{ik} are parameters, S_{ik} are elements of the overlap matrix, and

$[ij|kl]$ are two-center two-electron integrals for which indices ij are on one center and indices kl are on another center. P_{ij} and $D_{ij,kl}$ are the one- and two-electron density matrices, respectively, which in terms of spin density matrices are given by

$$P_{ij} = P_{ij}^{\alpha} + P_{ij}^{\beta} \quad (4)$$

$$D_{ij,kl} = P_{ij}P_{kl} - P_{ik}^{\alpha}P_{jl}^{\alpha} - P_{ik}^{\beta}P_{jl}^{\beta} \quad (5)$$

As can be seen from eq. (3) derivatives of the overlap ($\partial S/\partial m$) and two-center two-electron integrals ($\partial[ij|kl]/\partial m$) are needed to form the SCF contribution to the gradient. Traditionally, the basic integrals are evaluated in a local two-center system of coordinates and then rotated to the global Cartesian coordinate system. This is shown in eqs. (6)–(8), where indices i, j, \dots and a, b, \dots denote integrals calculated in the global and local coordinate systems, respectively, and X_{ia} is an element of a rotation matrix:

$$S_{ij} = \sum_{a,b} \Gamma_{ij}^{ab} S_{ab} \quad (6)$$

$$[ij|kl] = \sum_{a,b,c,d} \Gamma_{ijkl}^{abcd} [ab|cd] \quad (7)$$

$$\Gamma_{ijk\dots}^{abc\dots} = X_{ia}X_{jb}X_{kc}\dots \quad (8)$$

Because the integrals in the local coordinate system are functions of interatomic distance only, their derivative with respect to Cartesian coordinate m can be evaluated as:

$$\frac{\partial[ab|cd]}{\partial x} = \frac{\partial[ab|cd]}{\partial R} \times \frac{\Delta x}{R} \quad (9)$$

Based on this relationship it is possible to approximate values for integrals at coordinates $(\Delta x + \delta, \Delta y, \Delta z)$, $(\Delta x, \Delta y + \delta, \Delta z)$, $(\Delta x, \Delta y, \Delta z + \delta)$ by using a Taylor series expansion:

$$[ab|cd]^{(\delta)} = [ab|cd]^{(0)} + \frac{\partial[ab|cd]^{(0)}}{\partial m} \times \delta + \frac{1}{2} \frac{\partial^2[ab|cd]^{(0)}}{\partial m^2} \times \delta^2 + \dots \quad (10)$$

In eq. (10), superscript (0) denotes an integral evaluated at the default separation of $(\Delta x, \Delta y, \Delta z)$, whereas superscript (δ) represent an integral evaluated with a small displacement in either Δx , Δy , or Δz . We use this expression, truncated at first

order, to give approximate values for the overlap and two-center two-electron integrals at the displaced coordinates. To do this requires knowledge of the integrals and their derivatives with respect to R , but, in practice, only the derivative integrals need to be computed because the integrals are already evaluated prior to performing the SCF energy evaluation. Calculation of the two-center two-electron integral derivatives with respect to R is trivial, and code to perform this is available in MOPAC. For the overlap integral derivatives we used the following relationship¹⁸:

$$\begin{aligned} \frac{\partial S(n_1, n_2)}{\partial R} &= \frac{1}{R} \left\{ (n_1 + n_2 + 1) S(n_1, n_2) \right. \\ &\quad - ((n_1 + 1)(n_1 + \tfrac{1}{2}))^{1/2} S(n_1 + 1, n_2) \\ &\quad \left. - ((n_2 + 1)(n_2 + \tfrac{1}{2}))^{1/2} S(n_1, n_2 + 1) \right\} \quad (11) \end{aligned}$$

where $S(n_1, n_2)$ is an overlap integral between two orbitals with principal quantum numbers n_1 and n_2 .

Given approximate values for the two-center two-electron and overlap integrals at the displaced geometries and in the local coordinate system, their values in the global coordinate system are obtained by applying rotations according to eqs. (6)–(8). This is an identical procedure to that currently used in MOPAC, except that, in our case, the underlying integrals at the displaced geometries are approximate, hence the rotated integrals will also be approximate. For completeness the computational procedure required to evaluate gradients using the two-sided PRECISE scheme as implemented in MOPAC, but, with our approximate integrals, is as follows:

1. Overlap and two-center two-electron integrals for all pairs of atoms are evaluated in the local coordinate system and stored.
2. Integrals in the global coordinate system are obtained, by rotation [eqs. (6)–(8)], from those evaluated in the local coordinate system.
3. The electronic density matrix, P , is calculated by the usual SCF procedure.
4. For each pair of atoms:
 - (a) Derivative two-center two-electron and overlap integrals with respect to R , their internuclear separation, are evaluated.

- (b) Approximate values for the integrals at points with coordinates $(\Delta x \pm \delta, \Delta y, \Delta z)$, $(\Delta x, \Delta y \pm \delta, \Delta z)$, $(\Delta x, \Delta y, \Delta z \pm \delta)$ are computed using eq. (10) truncated to first order.
 - (c) Rotation matrices are computed at the six displaced coordinates and used to rotate the approximate integrals to the global coordinate system.
 - (d) The SCF two-center pair energy is computed at each displaced geometry and used in a two-sided finite difference formula to obtain a contribution to the total gradient.
 - (e) The derivative of the core repulsion energy with respect to R is computed analytically and used in eq. (2) to give derivatives with respect to Cartesian coordinates.
5. When all atom pairs have been computed the total gradient is complete.

In contrast to the above, the less accurate MOPAC default gradients are obtained by making the four displacements detailed earlier. (We also note that, because the hydrogen–hydrogen interactions involve just s functions there are no rotations involved, hence, for these interactions, the derivatives are in fact computed analytically.)

The advantage of the new scheme lies in the number of times the integrals need to be computed. In the original MOPAC gradient and for each pair of atoms the integrals are evaluated four times and four rotations are performed. Using the PRECISE option increases this to six integral evaluations and six rotations per atom pair. In contrast, the new procedure requires just one evaluation of the integral derivatives for both the default and PRECISE option, and either four or six rotations, respectively. Because evaluation of integral derivatives uses approximately the same number of operations as evaluation of the integrals, and rotations are slightly faster than integral evaluation, we may expect the new procedure to be up to twice as fast as the previous algorithm.

Accuracy

The original numerical MOPAC gradients are, in themselves, approximations to the analytical gradients, and are accurate to either first or second

order depending on whether the default or PRECISE scheme is used. The new scheme introduces another level of approximation and it is important to understand how this impacts on the overall accuracy of the numerical gradients. Denoting $E2_{scf}^{(\delta)}$ as the energy obtained by replacing the derivative integrals in eq. (3) with integrals evaluated at the displaced geometry, and expanding these according to eq. (1), we obtain:

$$\begin{aligned}
 E2_{scf}^{(\delta)} = & \sum_{i,j,a,b} P_{ij} \Gamma_{ij}^{ab(\delta)} \left([ab|ss_B]^{(0)} \right. \\
 & + \frac{\partial [ab|ss_B]^{(0)}}{\partial m} \delta + \frac{1}{2} \frac{\partial^2 [ab|ss_B]^{(0)}}{\partial m^2} \delta^2 \\
 & \left. + O(\delta^3) \right) \\
 & + \sum_{i,k} \beta_{i,k} \Gamma_{ij}^{ab(\delta)} \left(S_{ab}^{(0)} + \frac{\partial S_{ab}^{(0)}}{\partial m} \delta \right. \\
 & \left. + \frac{1}{2} \frac{\partial^2 S_{ab}^{(0)}}{\partial m^2} \delta^2 + O(\delta^3) \right) \\
 & + \sum_{i,j,k,l} D_{ij,kl} \Gamma_{ijkl}^{abcd(\delta)} \left([ab|cd]^{(0)} \right. \\
 & + \frac{\partial [ab|cd]^{(0)}}{\partial m} \delta + \frac{1}{2} \frac{\partial^2 [ab|cd]^{(0)}}{\partial m^2} \delta^2 \\
 & \left. + O(\delta^3) \right) \quad (12)
 \end{aligned}$$

The new algorithm truncates the Taylor series expansion at first derivatives, and therefore introduces an error at second order ($O(\delta^2)$) in $E2_{scf}^{(\delta)}$. This error is of the same order as that incurred by using the default “one-sided” finite difference scheme found in MOPAC, and should therefore not present a problem. Using the two-sided PRECISE option with the original MOPAC code, however, gives numerical gradients that are correct to second order. Thus, at first sight, it would appear that use of the above approximation is unjustified when using PRECISE MOPAC gradients. On closer inspection, however, this is not the case. The PRECISE MOPAC gradients are evaluated as:

$$\frac{\partial E2_{scf}^{(0)}}{\partial m} \approx (E2_{scf}^{(+\delta)} - E2_{scf}^{(-\delta)}) / (2\delta) \quad (13)$$

Substituting eq. (12) into eq. (13), and collecting the terms of order δ^2 , gives:

$$\begin{aligned} & \left\langle \frac{\partial E_{scf}^{(0)}}{\partial m} \right\rangle O(\delta^2) \\ &= \sum_{i,j,a,b} \sum_B P_{ij} Z_B (\Gamma_{ij}^{ab(+\delta)} - \Gamma_{ij}^{ab(-\delta)}) \\ & \quad \times \frac{1}{2} \frac{\partial^2 [ab|ss_B]^{(0)}}{\partial m^2} \delta^2 \\ & \quad + \sum_{i,k} \beta_{i,k} (\Gamma_{ij}^{ab(+\delta)} - \Gamma_{ij}^{ab(-\delta)}) \\ & \quad \times \frac{1}{2} \frac{\partial^2 S_{ab}^{(0)}}{\partial m^2} \delta^2 \\ & \quad + \sum_{i,j,k,l} D_{ij,kl} (\Gamma_{ijkl}^{abcd(+\delta)} - \Gamma_{ijkl}^{abcd(-\delta)}) \\ & \quad \times \frac{1}{2} \frac{\partial^2 [ab|cd]^{(0)}}{\partial m^2} \delta^2 \end{aligned} \quad (14)$$

All these terms involve differences between rotation matrices for a positive and negative displacement. The value of these is given approximately by:

$$(\Gamma_{ij}^{ab(+\delta)} - \Gamma_{ij}^{ab(-\delta)}) \approx 2 \frac{\partial \Gamma_{ij}^{ab(0)}}{\partial m} \times \delta \quad (15)$$

Eq. (15) is first order in δ and therefore eq. (14) is actually third order in δ , maintaining the overall accuracy of the PRECISE MOPAC gradients. As will be shown, this conclusion is also supported by numerical tests.

Analytical Gradients

Before considering use of the new scheme it is pertinent to consider the relative expense of numerical versus analytical gradients. Direct differentiation of eq. (7) gives:

$$\begin{aligned} \frac{\partial [ij|kl]}{\partial m} &= \sum_{a,b,c,d} \frac{\partial [ab|cd]}{\partial m} \Gamma_{ijkl}^{abcd(0)} \\ & \quad + \sum_{a,b,c,d} [ab|cd] \frac{\partial \Gamma_{ijkl}^{abcd(0)}}{\partial m} \end{aligned} \quad (16)$$

where:

$$\begin{aligned} \frac{\partial \Gamma_{ijkl}^{abcd(0)}}{\partial m} &= \frac{\partial X_{ia}}{\partial m} X_{jb} X_{kc} X_{ld} + X_{ia} \frac{\partial X_{jb}}{\partial m} X_{kc} X_{ld} \\ & \quad + X_{ia} X_{jb} \frac{\partial X_{kc}}{\partial m} X_{ld} + X_{ia} X_{jb} X_{kc} \frac{\partial X_{ld}}{\partial m} \end{aligned} \quad (17)$$

This expression requires the same integrals and derivatives as the new approximate numerical scheme, but differs in the number of times they must be rotated. For analytical derivatives, 15 rotations are required to obtain the three Cartesian derivatives associated with each atom pair, whereas, for the approximate scheme, either four or six rotations are required, depending on whether we compute the default or PRECISE gradient. Thus, the relative cost of the rotations required for the analytical and numerical methods is either 15:6 or 15:4. In practice, however, the relative difference is not this great, because for *sp* basis sets many of the elements of *X* are equal to 1, reducing the number of multiplications needed to perform the rotation.

Numerical Results

Although the new procedure for gradient computations has been implemented in MOPAC for the MNDO,⁹ AM1,¹⁰ and PM3¹¹ methods, we will only report results for the AM1 method here. All calculations were run on a 167-MHz Sun Ultrasparc workstation.

To validate the new algorithm, five different molecules were chosen and their gradients computed at some arbitrary point using the default and PRECISE numerical differentiation schemes with either the original or new approximate integrals. The resulting gradients are compared (Table I) with those computed analytically. Three comparisons are made, the gradient norm, the average deviation between the analytical and numerical gradients, and the maximum deviation. The gradient norm is defined as follows:

$$\text{Gradient norm} = \frac{1}{N} \left(\sum_{i=1}^{3N} G_i^2 \right)^{1/2}$$

where *N* is the number of atoms in the molecule.

The results show that the gradients obtained using the new procedure are very close to the original MOPAC gradients. When the default nu-

TABLE I.
Comparison of Original and New Gradient with Analytical Derivatives.^a

| Molecule ^b | Properties | Original Gradients | | New Gradients | |
|---|----------------|--------------------|---------|---------------|---------|
| | | Default | PRECISE | Default | PRECISE |
| Leu-enkephalin C ₂₈ N ₅ O ₇ H ₃₇ (0.5786) | Gradient norm | 0.5786 | 0.5786 | 0.5788 | 0.5786 |
| | Av. deviation | 0.0545 | 0.0001 | 0.0331 | 3e10-6 |
| | Max. deviation | 0.0712 | 0.0005 | 0.0658 | 5e10-6 |
| | Time (seconds) | 1.15 | 1.73 | 0.59 | 0.78 |
| Guanine / cytosine pair C ₉ N ₈ O ₂ H ₁₀ (13.8020) | Gradient norm | 13.8028 | 13.8020 | 13.8014 | 13.8020 |
| | Av. deviation | 0.0442 | 0.0001 | 0.0722 | 3e10-6 |
| | Max. deviation | 0.0600 | 0.0005 | 0.1007 | 4e10-6 |
| | Time (seconds) | 0.20 | 0.30 | 0.10 | 0.14 |
| Methotrexate C ₂₀ O ₅ N ₈ H ₂₀ (16.4565) | Gradient norm | 16.4562 | 16.4565 | 16.4570 | 16.4565 |
| | Av. deviation | 0.0630 | 0.00008 | 0.0512 | 3e10-6 |
| | Max. deviation | 0.0922 | 0.0006 | 0.1130 | 4e10-6 |
| | Time (seconds) | 0.59 | 0.90 | 0.30 | 0.41 |
| NADPH C ₂₁ O ₁₇ N ₇ P ₃ H ₃₀ (10.0513) | Gradient norm | 10.0513 | 10.0513 | 10.0512 | 10.0513 |
| | Av. deviation | 0.0647 | 0.0001 | 0.0322 | 3e10-6 |
| | Max. deviation | 0.0948 | 0.0002 | 0.0566 | 5e10-6 |
| | Time (seconds) | 1.28 | 1.94 | 0.65 | 0.89 |
| Valinomycin C ₅₄ O ₁₈ N ₆ H ₉₀ (8.8970) | Gradient norm | 8.8969 | 8.8970 | 8.8970 | 8.8970 |
| | Av. deviation | 0.0759 | 0.0008 | 0.0429 | 0.0008 |
| | Max. deviation | 0.0928 | 0.0019 | 0.0994 | 0.0024 |
| | Time (seconds) | 5.06 | 7.58 | 2.56 | 3.44 |

^a All gradients are given in units of kcal / mol · Å.
^b The norm of the analytic gradient is shown in parentheses.

merical differentiation is used, the new gradients are, on average, closer to the analytical gradients than the original MOPAC gradients, although the maximum deviation tends to be larger. With the PRECISE option, the two schemes are nearly identical. This is highlighted in Table II where we show the difference between the original PRECISE gradients and those obtained using the new approximate integrals; the deviations are of the order of 0.0001 kcal/mol · Å or more then 1000 times smaller than the gradients themselves. Also given in Table I is the time required to compute the gradients. This clearly shows the new algorithm to be much faster than the original one.

TABLE II.
Deviation of the New PRECISE Gradient from Original MOPAC PRECISE gradient.

| Molecule | Average | Maximum |
|-------------------------|---------|---------|
| Leu-enkephalin | 0.0001 | 0.0005 |
| Guanine / cytosine pair | 0.0001 | 0.0005 |
| Methotrexate | 0.0001 | 0.0006 |
| NADPH | 0.0001 | 0.0002 |
| Valinomycin | 0.0003 | 0.0006 |

To verify further the accuracy of the new method we performed geometry optimizations on all five molecules using the standard geometry optimization algorithm found in MOPAC. The results obtained (Table III) show both the new and the original MOPAC gradients to be performing equally well. Specifically when the default numerical gradients are used, the new method gives lower energies for two of the test cases (the guanine/cytosine base pair and methotrexate), but higher energies for the remaining three. The absolute deviation in the heats of formation is, however, only 0.46 kcal/mol. With the PRECISE option we obtained similar results, with the new gradients giving a much lower energy for the leu-enkephalin molecule (by nearly 3 kcal/mol), a slightly higher energy for the guanine/cytosine base pair, and higher energies for the remaining three systems.

The aforementioned optimization results are not surprising, because the exact path taken during optimization and associated termination point is very sensitive to the values of the energy and gradient at each step. In MOPAC with the default, numerical gradient optimizations often terminate when the search routine fails to find a point of lower energy. Using more accurate gradients gen-

TABLE III.
Results of Geometry Optimization Using New and Original Gradients.

| Molecule | Property | Original Gradients | | New Gradients | |
|---|---------------------------|--------------------|---------|---------------|---------|
| | | Default | PRECISE | Default | PRECISE |
| Leu-enkephalin | ΔH_f (kcal / mol) | -249.01 | -250.97 | -248.99 | -253.76 |
| C ₂₈ N ₅ O ₇ H ₃₇ | Gradient norm | 0.4719 | 0.1190 | 0.1580 | 0.1022 |
| | Number of steps | 35 | 134 | 44 | 321 |
| | ΔH_f (kcal / mol) | 40.70 | 39.43 | 40.52 | 39.45 |
| Guanine / cytosine pair | Gradient norm | 0.2893 | 0.0828 | 0.2641 | 0.0652 |
| | Number of steps | 48 | 181 | 58 | 148 |
| | ΔH_f (kcal / mol) | -26.34 | -30.49 | -26.80 | -30.15 |
| Methotrexate | Gradient norm | 0.4194 | 0.0757 | 0.3696 | 0.1598 |
| | Number of steps | 59 | 564 | 57 | 448 |
| | ΔH_f (kcal / mol) | -857.08 | -866.82 | -857.01 | -865.35 |
| C ₂₁ O ₁₇ N ₇ P ₃ H ₃₀ | Gradient norm | 0.3426 | 0.0538 | 0.4555 | 0.1260 |
| | Number of steps | 60 | 1087 | 59 | 636 |
| | ΔH_f (kcal / mol) | -836.21 | -844.88 | -836.19 | -844.39 |
| Valinomycin C ₅₄ O ₁₈ N ₆ H ₉₀ | Gradient norm | 0.1390 | 0.0261 | 0.1443 | 0.0423 |
| | Number of steps | 58 | 2234 | 57 | 1081 |
| | | | | | |

erally solves this problem and enables the optimization to terminate by meeting one or more of the convergence criteria. Hence, some differences in the results are expected. The overriding conclusion must be that use of the new gradients does not drastically effect the characteristics of the optimization algorithm.

Conclusions

A new algorithm has been proposed for the evaluation of numerical gradients in semiempirical codes. The new method provides gradients of similar accuracy to those currently available, but at approximately half the computational cost. The new method has been implemented into MOPAC and tested on a variety of molecules.

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